REMARKS/ARGUMENTS

Applicants would like to thank Examiner Wegert for telephone conference with Anna Barry on August 24, 2004 to address the ambiguities regarding to page/paragraph numbers cited in the instant Office Action.

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application and were rejected on various grounds. With this amendment, Claims 28-32, 36-37 and 41-43 have been canceled without prejudice, Claims 33-35, 38-39 and 44 have been amended, and new Claims 48-54 have been added.

Claims 33-35, 38-40 and 44-54 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. In addition, new Claims 48-54 are fully supported by the specification as originally filed. Support for new Claims 48-54 can be found at least on p. 237, lines 23-26, on p. 282, lines 12-19 and on p. 308, line 38 to p. 309, line 7 of the specification.

Specification

In response to the Examiner's request, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code.

Applicants respectfully submit that all references to page and line numbers made throughout this response will be based on the present application's specification as filed, an electronic copy of which is available from the PTO website.

Priority Determination

The Examiner stated that the effective filing date for the application is September 1, 1999, the filing date of PCT/US99/20111.

Applicants rely on the gene amplification assay (Example 143) for patentable utility which was first disclosed in U.S. Provisional Application No. 60/162,506, filed October 29, 1999, priority to which has been claimed in this application.

As will be shown, the disclosure of the instant application, which is similar to that of the earlier-filed application (U.S. Provisional Application No. 60/162,506), provides the support required to establish utility for the claimed protein, for example, in detecting over-expression or absence of expression of the PRO1755 polypeptide. Accordingly, Applicants submit that the subject matter of the instant claims is supported by the disclosure in U.S. Provisional Application No. 60/162,506. Therefore, the effective filing date of this application is October 29, 1999, the filing date of U.S. Provisional Application No. 60/162,506.

Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph

Claims 28-47 are rejected under 35 U.S.C. §101, allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." The examiner asserts that "the specification does not disclose a function for the nucleotide of SEQ ID NO:351, encoding the polypeptide of SEQ ID NO:352, in the context of the cell or organism."

Claims 28-47 are also rejected under 35 USC 112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ..., one skilled in the art would not know how to use the claimed invention."

The Examiner specifically notes that "there is no disclosure of particular disease states correlating to an alteration in levels or forms of the polypeptide such that the claimed polynucleotides encoding SEQ ID NO: 352 could be used as a diagnostic tool."

Applicants respectfully disagree with and traverse the rejection.

Examiner alleges that the specification asserts the following four utilities for the claimed polynucleotide and polypeptide encoded by the claimed polynucleotide:

1) For use in the construction of "knock-in" or "knock-out" organisms.

2) In assays to screen for compounds capable of modifying the interaction between receptor and ligand.

3) To make antibodies to the polypeptide encoded by the polynucleotide of SEQ ID NO: 351.

4) To treat cancer.

See pages 4-5 of the instant Office Action.

Applicants note that portions of the instant Office Action discuss the alleged lack of utility for the PRO1755 polypeptide and the antibodies. (For example, see pages 5-6). Applicants respectfully submit that present application is directed to nucleic acids. Nevertheless, Applicants maintain that the utility is provided for the polypeptides and antibodies in the present application.

Applicants submit that the cancellation of Claims 28-32, 36-37 and 41-43 renders the rejection of these claims moot.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is *a preponderance of the totality of the evidence* under consideration. *In re* Oetiker, 977 F.2d 1443,

1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that *it is more likely than not* that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a "substantial" utility." M.P.E.P. 2107.01, emphasis added. Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." M.P.E.P. 2107 II(B)(1)(ii). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Revised Interim Utility Guidelines Training Materials, 1999.

Proper Application of the Legal Standard

Applicants submit that the invention defined by the presently amended claims has specific, substantial and credible utility for the nucleic acids encoding the PRO1755 polypeptide.

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 143 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan PCR. Table 8 shows the resulting gene amplification data. Further, Example 143 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc. The Examiner has noted that the nucleic acids encoding PRO1755 had ΔCt value of > 1.0 for 3 primary lung tumors (LT16, LT18 and LT22) and five primary colon tumors (CT2, CT8, CT10, CT12 and CT14). (See Office Action, page 5). PRO1755 showed approximately 1.18-1.36 ΔCt units which corresponds to $2^{1.18}$-$2^{1.36}$ fold amplification or 2.266 fold to 2.567-fold amplification in lung tumors. PRO1755 also showed approximately 1.15-2.35 ΔCt units which corresponds to $2^{1.15}$ - $2^{2.35}$ fold amplification or 2.219 fold to 5.098-fold amplification in colon tumors.

It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that polynucleotide of SEQ ID NO: 351 encoding the PRO1755 polypeptide is a diagnostic marker of human lung and colon cancer.

Accordingly, the claimed invention has a specific, substantial and well established utility that is well described in the specification.

Applicants respectfully submit that based on the teachings of Example 143 and the general knowledge available in the art at the priority date of the invention, one skilled in the art would be able to practice the claimed invention in its full scope without any undue experimentation. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983),

aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01.

Furthermore, based on the instant disclosure and the advanced knowledge in the art at the time of filing, one skilled in the art would know exactly how to make and use these nucleic acids for the diagnosis of lung and colon tumors; for example, by using diagnostic methods based on hybridization to such amplified sequences.

In view of the above, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-47 are rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention." The Examiner asserts that "the specification does not teach functional or structural characteristics of all claimed polynucleotides. The description of one polynucleotide encoding a PRO polypeptide (SEQ ID NO: 352) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides."

Applicants submit that the cancellation of Claims 28-32, 36-37 and 41-43 renders the rejection of these claims moot.

In view of the discussions above regarding the utility of the polynucleotides, Applicants respectfully submit that Claims 33-35, 38-40 and 44-47 satisfy the written description requirement, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application. Hence, the present rejection should be withdrawn.

Deposit Requirement

Claims 28-47 are rejected under 35 U.S.C. §112, first paragraph, allegedly for lack of written description. The Examiner states that the specification indicates that a deposit of the

nucleic acid molecules was made under the Budapest Treaty, but Applicants have failed to provide a copy of the deposit receipt. In response, Applicants enclose herewith a copy of the deposit receipt indicating that DNA76396-1698 deposit, ATCC Deposit No. 203471, was made by Applicants on November 17, 1998.

The Examiner also alleges that the address for the depository, for example on page 13 of the specification, is missing. Applicants respectfully submit that Applicants cannot find the location on page 13 or in any of the adjacent pages wherein the depository address is missing as indicated by the Examiner. However, Applicants respectfully point the Examiner to page 517, line 1 of the specification wherein the specification clearly discloses that the deposit was made under the Budapest Treaty. Applicants submit that the specification correctly provides the accession number for the deposit, the date of the deposit, the description of the deposited material, and the name and *address* of the depository. See starting on paragraph page 517, line 1 of the specification.

Applicants further submit that the specification has been amended to incorporate the requisite assurances that the deposit will be maintained "for 30 years from the date of deposit and for at least five (5) years after the most recent request for the furnishing of a sample of the deposit received by the depository" and to recite that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Accordingly, Applicants believe that the present rejection should be withdrawn.

Claim 28-32, 36-37 and 41-43 have been cancelled without prejudice and hence, the rejection to these claims is believed to be moot, and should be withdrawn.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

Claims 28-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point our and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that Claims 28-47 are rendered indefinite because of the phrase "extracellular domain".

Since the terms "the extracellular domain" and "extracellular domain ... lacking its associated signal peptide" are no longer present in Claims 33 (and, as a consequence, those claims dependent from the same), the rejection is believed to be moot, and should be withdrawn.

Claims 28-32, 36-37 and 41-43 have been cancelled without prejudice and hence, the rejection to this claim is believed to be moot, and should be withdrawn.

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2830 P1C64**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 31, 2004

By: _____
Anna L. Barry (Reg. No. 51,436)

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